Mesenchymal stem cells derived from human gingiva are capable of immunomodulatory functions and ameliorate inflammation-related tissue destruction in experimental colitis.

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Public Summary:
Mesenchymal stem cells (MSC) have the capacity to self-renew and differentiate into different cell lineages, including mesodermal, endodermal and ectodermal cells. Originally isolated from bone marrow (BM), similar subsets of multipotent MSC have also been identified in skin, adipose tissue, tendon lung, heart and liver, placenta, amniotic fluid, and umbilical cord blood. In addition, several populations of MSC have been identified in various dental tissues, including dental pulp stem cells (DPSC), stem cells of human exfoliated deciduous teeth (SHED), periodontal ligament stem cells (PDLSC), dental follicle precursor cells (DFPC), and stem cells from apical papilla (SCAP). Asides from the abilities of self-renewal and multipotent differentiation, MSC commonly express specific genes for embryonic stem cells, such as Octamer-4 (Oct-4) and stage specific embryonic antigen-4 (SSEA-4), and share a similar expression profile of cell surface molecules, such as Stro-1, SH2 (CD105), SH4 (CD73), CD90, CD146, CD29, but typically lack hematopoietic stem cell (HSC) markers, such as CD34 and CD45. At the functional level, MSC displays chemotactic properties similar to immune cells in response to tissue insult and inflammation, thus exhibiting tropism for the sites of injury via production of anti-inflammatory cytokines, and anti-apoptotic molecules. These unique characteristics of MSC make them attractive candidates for the development of novel allogeneic cell-based therapeutic strategies in harnessing inflammation in the repair or regeneration of a variety of damaged tissues. A growing body of evidence has demonstrated that bone marrow derived MSC (BMMSC) are non-immunogenic and more importantly, display profound immuno-modulatory and anti-inflammatory capabilities. BMMSC exhibit immuno-modulatory effects via inhibiting the proliferation and function of several major immune cells such as T and B lymphocytes, natural killer (NK), and dendritic,cells, via direct cell-cell contact or/and soluble cytokines. To date, several soluble factors either produced constitutively by MSC or as a result of cross-talks with target immune cells, have been attributed to the immuno-modulatory properties of MSC, including transforming growth factor (TGF)-β1, hepatocyte growth factor (HGF), interleukin (IL)-10, prostaglandin (PEG)-2, nitric oxide (NO), and indoleamine-2, 3-dioxygenase (IDO). Interestingly, tumor necrosis factor (TNF)-α and interferon (IFN)-γ, two important pro-inflammatory cytokines secreted by activated T cells, have been demonstrated to stimulate PGE-2, TGF-β1, HGF, NO, and IDO expression by MSC. These findings suggest that TNF-α and IFN-γ serve as critical feedback signal molecules in the cross-talks between immune cells and MSC with potential role in MSC-mediated immunosuppressive activities. Furthermore, the immunomodulatory and anti-inflammatory effects of MSC have been demonstrated in the treatment of several animal disease models, including graft-versus-host disease (GvHD), diabetes, rheumatoid arthritis (RA), autoimmune encephalomyelitis, systemic lupus erythematosus (SLE), periodontitis, intestinal and bowel disease (IBD), and sepsis. These studies provided convincing evidences that BMMSC-based therapy may offer potential anti-inflammatory and immunomodulating effects in the treatment of a variety of inflammatory and autoimmune diseases. Here, we isolated a new population of stem cells from human orofacial tissue gingiva, a tissue source easily accessible from the oral cavity, namely GMSC, which exhibited clonogenicity, self-renewal, and multipotent differentiation capacities. Most importantly, GMSC were capable of immunomodulatory functions, specifically suppressed peripheral blood lymphocyte proliferation, induced expression of a wide panel of immunosuppressive factors including interleukin 10 (IL-10), indoleamine 2,3-dioxygenase (IDO), nitric oxide (iNOS), and cyclooxygenase-2 (COX-2) in response to the inflammatory cytokine, interferon-γ (IFN-γ). Cell-based therapy using systemic infusion of GMSC in experimental colitis significantly ameliorated both clinical and histopathological severity of the colonic inflammation, restored the injured gastrointestinal mucosal tissues, reversed diarrhea and weight loss, and suppressed the overall disease activity in mice. The therapeutic effect of hGMSC was mediated, in part, by the suppression of inflammatory infiltrates and inflammatory cytokines/mediators at the colonic sites. Taken together, GMSC can function as an immunomodulatory and anti-inflammatory component of the immune system in vivo and is a promising cell source for cell-based treatment in experimental inflammatory diseases.

Scientific Abstract:
Aside from the well-established self-renewal and multipotent differentiation properties, mesenchymal stem cells exhibit both immunomodulatory and anti-inflammatory roles in several experimental autoimmune and inflammatory diseases. In this study, we isolated a new population of stem cells from human gingiva, a tissue source easily accessible from the oral cavity, namely, gingiva-derived mesenchymal stem cells (GMSCs), which exhibited clonogenicity, self-renewal, and multipotent differentiation capacities. Most importantly, GMSCs were capable of immunomodulatory functions, specifically suppressed peripheral blood lymphocyte proliferation, induced expression of a wide panel of immunosuppressive factors including IL-10, IDO, inducible NO synthase (iNOS), and cyclooxygenase 2 (COX-2) in response to the inflammatory cytokine, IFN-gamma. Cell-based therapy using systemic infusion of GMSCs in experimental colitis significantly ameliorated both clinical and histopathological severity of the colonic inflammation, restored the injured gastrointestinal mucosal tissues, reversed diarrhea and weight loss, and suppressed the overall disease activity in mice. The therapeutic effect of GMSCs was mediated, in part, by the suppression of inflammatory infiltrates and inflammatory cytokines/mediators and the increased infiltration of regulatory T cells and the expression of anti-inflammatory cytokine IL-10 at the colonic sites. Taken together, GMSCs can function as an immunomodulatory and anti-inflammatory component of the immune system in vivo and is a promising cell source for cell-based treatment in experimental inflammatory diseases.

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